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Arthropods in Cosmetics, Pharmaceuticals and Medicine: A Review

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Abstract

Apart from food, other important needs in the care of human bodies are cosmetics and drugs. For long the latter two are obtained from chemical formulations and phytochemicals (commonly used in Ethnomedicine), use of bioactive compounds from insects (i.e. “ento medicine” and “ento cosmetics”) is a recent development in research, even though the bioactive compounds were discovered long ago. This chapter is a review on a number of substances extracted from various insect species that are useful in cosmetics, pharmaceutical industries as well as those that form part of prescription for healing in orthodox and traditional medicine. The review is based on information from scientific reports, Google, e-library, textbooks. A number of substances were found to have been incorporated into cosmetic and pharmaceutical products and as part of prescriptions for healing in orthodox medicine, many others at elementary stages of investigation, purification and development. The findings showed that insects have a lot of bioactive substances that need to be harnessed for the good man.

Keywords: arthropods, uses, cosmetics, pharmaceuticals, medicine

1. Introduction

Arthropods, a word coined from two Greek words: “arthron” meaning “joint” and “pous”(podos) meaning “foot” (the two together means “jointed legs”) comprise all animals with jointed legs including insects, spiders, mites, ticks, and scorpions. Radis-Baptista and Konno [1] stated that the myriad of animals under this phylum are grouped into four subphyla namely Chelicerata, (Arachnids), Crustacea, Myriapoda (Centipedes) and Hexapoda (insects). A lot of these arthropods produce some chemical substances and/or venom to protect themselves from danger of being killed or being captured, while some produce substances for yet to be identified purposes. Radis-Baptista and Konno [1] noted that thousands of arthropods species ranging from arachnids (spiders and scorpions), to hymenopterans (ants, bees and wasps) and myriapods (centipedes) are venomous and utilize

their venoms for chemical ecological warfare that includes individual and colonial defense, predation and paralysis of coexistent species to nourish their brood. The arthropods inject their self-produced venom or other substances into their victims through bites, stings or spray of aerosol-like chemicals. Scientists have shown [2–4] that these arthropods secretions/venoms may include toxins (e.g., inorganic or organic compounds, alkaloids, etc.) and other compounds (e.g., histamines, enzymes) [5], that may enhance the effectiveness or “spread” of the toxins. These arthropod secretions (whether venom or other substances) contain a number of chemical substances useful for cosmetics, pharmaceutical and nutraceutical products, as well as medicine. This paper is a review of chemical substances and venom of some arthropods useful in the cosmetic, pharmaceutical industries as well as those utilized in orthodox and traditional medicine.

2. Arthropods and cosmetics

2.1 Cochineal or carmine (Hemiptera: true bugs)

Cochineal or carmine is a red insect dye from female scale insect *Dactylopius coccus*, a cactus-eating insect native to tropical and subtropical regions of South America and Mexico. It was earlier used for dyeing cloth by the Aztecs, but today, it is used as a dye in foods, cosmetics, drugs, and dyeing of textiles. The red pigment (carmine) is made from crushing female cochineal beetles, and it reportedly takes 70,000 to 100,000 dead females to produce 1kg of cochineal dye [Business insider 2011]. The female cochineal beetles gain a red colour through their diet of red berries, and so produce red carminic acid when threatened. In the cosmetics industry, cochineal is used to dye lipstick, blush, and eye shadow. It creates bright, bold and deep red colors. Today, the cochineals are harvested mainly in Peru and the Canary Islands on plantations of prickly pear cacti which is the preferred host of the bug. The natives sun-dry the insects, crush it and dunk in an acidic alcohol solution to produce carminic acid, the pigment that eventually becomes carmine or cochineal extract, depending on the processing method adopted. A number of works [6], have been going on how to increase the yield of carmine from the *Dactylopius coccus*.

2.2 Lac and shellac from scale insects (Hemiptera)

Lac is a the resinous secretions from a number of species of lac scale insects, *Laccifer lacca*, and most of it is produced in India, Lac is an important ingredient of many items, including floor polishes, shoe polishes, insulators, various sealants, printing inks, and varnish. In the cosmetic industry, it is used mainly for nail polish remover. Juliane [7] described the three processes involved in the production of shellac from lac. According to him, cultivation begins when the farmer gets a stick containing eggs ready to hatch and ties it to the tree to be infested. Thousands of lac insects colonize the branches of the host tree and secrete the resinous substance, the coated branches are cut out and harvested as sticklac. The harvested sticklac is sieved and subjected to a number of washings to remove impurities of all kinds, resulting in a purer form called seedlac. However, seedlac still contains 3-5% of impurity, further removal of impurities by heat treatment or solvent extraction results in the product called shellac. Shellac is therefore a processed secretion of the lac insect.

Raman [8] described shellac as a resin secreted by the female lac bug on trees in the forest of India and Thailand, processed and sold as flakes and dissolved in alcohol to form liquid shellac. *Tachardia lacca* or *Kerria lacca*. In the cosmetic industry,

the shellac is used for personal care products in hair sprays, eyeliners and mascara. Das [9] stated that shellac is a common ingredient in cosmetics such as mascara, lipsticks, nail polish and hairsprays. This is because shellac has the ability to hold the ingredients together in a compressed tablet or cake. It also keeps an emulsion from getting separated into water-soluble and oil soluble components, so it helps the hair hold its style by inhibiting the hair's ability to absorb moisture (i.e. shellac is non hygroscopic in nature). The Cosmetic Ingredient Review (CIR) panel has assessed shellac's safety and concluded that cosmetic-grade-shellac is safe for use in personal care and cosmetic product formulations up to 6%. From 1997 to 2002 Ken Golz-Berner has patented seven cosmetic products containing Shellac in various percentages.

2.3 Insect oil in cosmetic uses

2.3.1 Cosmetic oils from some dipterans

Rebecca Guenard a columnists writing in Olio, an Inform column of Inform Magazine that highlights research, issues and technologies of interest in fats and oil stated that fats and oil are major components of cosmetics, she further stated that linolenic acid heals dryness while triglycerides soften the skin. According to her report, skin care cream formulators earlier depended on mink oil as a source of these ingredients, but ethical considerations led to a shift to Macadamia nut oil with a similar fatty acid profile. However, competition with food use also limited Macadamia oil application in cosmetics thus the current interest in insect oil. A team of researchers from Thomas Moore University College and University of Antwerp both in Belgium assessed the usefulness of oil from three insect species: Black soldier fly (BSF) (*Hermetia illucens*), locust (*Locusta migratoria*) and the house cricket (*Acheta domesticus*) as an alternative source for the production of fats for cosmetics. The research was reported in [10] and they discovered that insect fats contained shelf life limiting phospholipids, which they were able to remove with a degumming procedure. After a gamut of tests and trials, the fats after extraction and refining were used in hand cream formulations and compared with conventionally used mink and plant derived oils. The fatty acid analysis showed that BSF contains >60% of lauric acids making it less suitable as a skin care product, whereas locust and cricket fats are rich in C16 and C18 fatty acids which makes them more suitable. However, the phospholipids and free fatty acids were found to be higher compared to commercially refined oils so they need to be removed by appropriate refining protocols, odor and colour also need to be removed for better applicability. They therefore concluded that with further refining locust and cricket oil would lose their colour and odour and become useful as a cosmetic product. Recently, a US company launched the world's first youth generating face oil containing insect oil extract by name Point68. The oil was developed as a joint venture between SIBU® and insect industry professional Josh Galt. Point 68 is reported to be a luxury face oil formulated to improve skin hydration with cellular healing and rejuvenation.

2.3.2 Honey and beeswax as cosmetic resources (Hymopterans)

Ediriweera and Premarathna [11] gave a long list of cosmetic uses of honey and beeswax in the beauty industry as a skin moisturizer, softener and a healer of skin tissue.

- **Face wash:** A small quantity of lemon juice is mixed with 5ml of bee's honey and applied to the face before washing. This is used as a home remedy

- **Facial cleansing scrub:** 5g of almond seed powder is mixed with 5ml of bee's honey, scrub softly and then wash [12]
- **Facial smoothness improver:** A tablespoon of honey is whisked together with white of an egg, 1 teaspoon of glycerine and 1/4 cup of flour makes an excellent firming mask. Just smooth on the face, leave on 15 min, and rinse off with warm water [12]
- **Facial softness improver:** One or two tablespoons of honey is mixed with one-third cup finely ground oatmeal. A teaspoonful of rose water is then added. This is used to clean the face thoroughly. This is spread evenly over the face. Allow to stay for 10 min to 1.5 hrs. Clean off with a soft washcloth and warm water, then rinse with cold water
- **Facial moisturizing pack:** 2 tablespoons of honey is mixed with 2 teaspoons of whole milk. This is applied over the face and allows it to stay for 15mins. It is then rinsed off with warm water, and then with cold water.
- **Pimples:** Honey is applied direct on pimples
- **Cracked lips:** Honey is applied on cracked lips
- **Lotion for dry patches of skin:** 5ml of bee's honey is mixed with 5ml of olive oil and 2.5 ml of lemon juice. It is applied on the skin and washes after 15 min.
- **Hair lustre:** 5ml of bee's honey is mixed with 4 cups of warm water. It is used as a hair rinse.
- **Conditioner:** 10 ml of olive oil is mixed with 5ml of bee's honey and applied on hair. It is washed after 15 min.

Burlando and Cornara [13] opined that in cosmetics preparations, honey exerts emollient, humectant, soothing and hair conditioning effects, while keeping the skin juvenile, retarding wrinkle formation, regulating pH and preventing pathogenic infections. According to them, honey based cosmetics products include lip ointment, cleansing milks, hydrating creams, after sun, tonic lotions, shampoos and conditioners ranging from 1 to 10% honey inclusion, though some products can contain up to 70% honey when mixed with oils, gels and emulsifiers or polymer entrapments.

2.3.3 Sericin from silkworm (*Lepidoptera*): a natural moisturizer in cosmetic products

Silkworm moth (*Bombyx mori*) is a lepidopteran, whose caterpillar is involved in production of silk during the process of cocoon formation. Silk is made up two proteins: fibroin (70-80%) and sericin (20-30%). Fibroin is the structural and fibrous part of the silk, while sericin is the gummy coating that gums the fibres and makes them stick to each other. Kunz *et al.* [14] discussed extensively on the use of sericin in cosmetics formulations such as creams and shampoos. Voegeli *et al.* [15] reported that inclusion of sericin in creams lead to hydration, elasticity of the skin thus leading to anti-aging and anti-wrinkle effects. Yamada *et al.* [16] also reported sericin in creams help to prevent nails from chapping and brittleness.

These applications are especially due to presence of amino acids with hydrophilic side groups (80%) such as serine (30-33%) which has large capacity to absorb water. Padawar *et al.* [17] cited in [14] studied in-vivo moisturizing effect of sericin on human skin and found its action to decrease the impedance and increase in the level of hydroxyproline and hydration of epidermal cells. The increase in hydration was attributed to the occlusive effect of sericin which prevented the transepidermal water loss, responsible for skin dryness. Sharma [16] stated that industrial production of one ton of silk yields 200kg of sericin and that sericin is isolated from cocoons of three types of silkworm: *Bombyx mori* (Mori), *Antheraea assamensis* (Muga) and *Philosamia ricin* (Eri). According to her Muga sericin embedded cream could be used for topical skin care application as a potential therapeutic to protect skin against UV radiation –induced inflammation, oxidative damage of epidermal keratinocytes, aging, wrinkling, preventing skin roughness, enhancing the skin elasticity and moisture [18, 19].

2.4 Arthropods and pharmaceuticals

2.4.1 Antimicrobial peptides (AMP) in wasp, ants and other arthropods

Insects are major sources of antimicrobial peptides/proteins (AMPs) which are cationic and comprise less than 100 amino acids [20–22] (**Table 1**). Their AMPs enable them to form resistance against bacterial infections. Antimicrobial peptides are short immunity related proteins that can fight bacteria, viruses, fungi and parasites [25] (**Figure 1**). According to them, AMP are secreted from cells and tissues that contribute to host innate immunity such as the haemocytes or the fat body and could be a valuable alternative antibiotics especially in this era of growing antimicrobial resistance [22, 25].

Dipteran species	Maggot factors	Activity against
<i>Sarcophaga peregrina</i>	Sarcotoxin 1A	Gram-negative bacteria
<i>Sarcophaga peregrina</i>	Sapecin B , Defensin A	Gram-positive bacteria, MRSA, fungi, cancer cells
<i>Drosophila melanogaster</i>	Cecropin A, B, C	Gram-negative bacteria, Gram-positive bacteria, fungi
<i>Phormia terranova</i>	Defensin A	Gram-positive bacteria
<i>Lucilia sericata</i>	Lucifensin	Gram-positive bacteria, MRSA
<i>Calliphora vicina</i>	Alloferon 1	Viruses and anti-cancer with cytokine activity
<i>Lucilia sericata</i>	p-hydroxybenzoic acid p-hydroxyphenylacetic acid Octahydro-dipyrrolo [1,2-a;10,20-d] [1,2-a;10,20-d]	Bacteria
<i>Lucilia sericata</i>	Seraticin	Bacteria, MRSA
<i>Sarcophaga peregrina</i>	5-S-GADa	Bacteria and anti-cancer

Source: Yi *et al.*, [23, 24].

Table 1.
Anti-bacterial and anti-cancer factors produced by Dipteran larva.

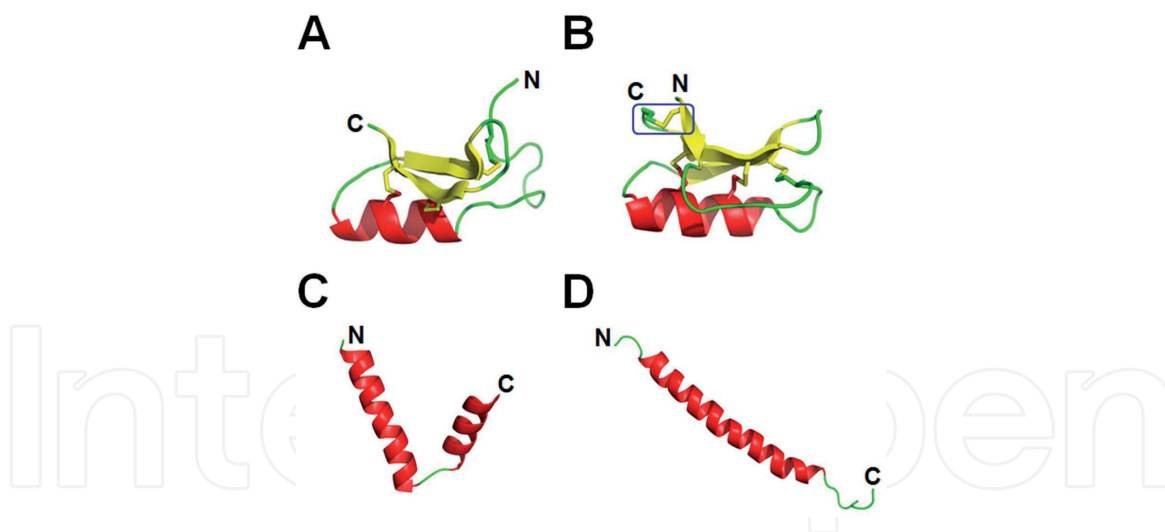


Figure 1.

Structures of an insect defensin, drosomycin, cecropin, and moricin. (A) *Protaphormia terraenovae* defensin (B) *Drosophila melanogaster* drosomycin (C) *Papilio xuthus* papiliocin (cecropin) (D) *Bombyx mori* moricin. Source: Yi et al, [23].

Reported on a number of antimicrobial substances found in insects [26]. The examples they gave included alloferon, an antimicrobial compound produced by blow fly larva, used as an antiviral and antitumor agent in South Korea and Russia and a compound sourced from the venom of the wasp *Polybia paulista* capable of killing cancer cells without harming normal cells. Ant venom can inhibit bacteria such as *Enterococcus faecalis* and *Listeria monocytogenes*. The types of antimicrobial peptides isolated from ants vary between ant species (e.g., polysulin I and II from the Jack jumper ant and solenopsins from the fire ant). In ancient times and today in some parts of Mexico, venom from red harvester ants is used to treat arthritis-like diseases (i.e., ants were placed on the affected areas and allowed to sting) [27].

Attacins another antimicrobial substance found in reasonable amount in *Heliothis virescens*, *B. mori* and *Hyphantria cune* that are active against gram negative bacteria such Gram-negative *E. coli* and *Citrobacter freundii* as well as the fungus *Candida albicans* [28]. Moricin was first isolated from *B.mori* larva, and can be found in other lepidoptera insects. Moricins have activity against Gram-negative and Gram positive bacteria [29], *Galleria mellonella* also show high activity against filamentous fungi and yeast [30].

The antimicrobial substance in wasp venom is mastoparan and it is found to be highly effective in decimating microbes, however, the high degree of damage to mammalian cells has prevented its use as a therapeutic compound. Other compounds found in wasp venom (e.g., eumenine-mastoparan, aumenitin, protonectin, paulistine) are being explored for their antibacterial properties and seem to have a minimal effect on mammalian cells.

Apart from insects, antimicrobial substances have also been extracted from the venom of other arthropods. A good example is lysosin-I from wolf spider (*Lycosa singoriensis*) venom which can inhibit bacteria such as *Shigella dysenteria* and *Staphylococcus aureus*. Budnik et al [31] stated that *Lycosa singoriensis* contain antimicrobial properties (lycocitin 1, 2, 3) that can inhibit the growth of gram positive and gram negative bacteria. Another important one is scolopin I, scolopin II, scolopendrin I (antibacterial peptide compounds) found in Chinese red-headed centipede [2].

Other insects with antimicrobial properties and the major molecules listed in [32] including:

Insect Molecule with AMB	Property	Author
<i>Ixodes persulcatis</i>	Persulcatusin	[33]
<i>Spodoptera Kitura</i>	Cecropin like peptides	[34]
<i>Tetramorium bicarinatum</i>	Bicarinalin	[35]
Callifora vicina	Alloferon	[36]
<i>Hermetia illucens</i>	Trx-Stomoxyn ZH I	[37]
<i>Galleria mellinella</i>	Apolipophorin III	[38]

2.4.2 *Insects with angiotensin converting enzyme (ACE) inhibitors*

Angiotensin Converting Enzyme (ACE) is a widely distributed zinc metalloproteinase that represents the final enzymatic step in the lysis of angiotensin I to produce angiotensin II. Enzyme (ACE) is a central component of the renin-angiotensin system (RAS) which controls blood pressure by regulating the volume of fluids in the body i.e. it converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. According to Riordan [5] ACE I is a monomeric, membrane bound zinc and chloride dependent peptidyl dipeptidase that catalyzes the conversion of decapeptide angiotensin I to the octapeptide angiotensin II by removing a carboxyl terminal dipeptide. Riordan [5] also stated that ACE also known as peptidyl-dipeptidase A or Kininase II was first isolated in 1956 and shown to be to be chloride dependent metalloenzyme that cleaves dipeptide from the carboxyl terminus of the decapeptide angiotensin I to form a potent vasopressor (blood vessel constrictor) angiotensin II.

Herman et al. [39] reported the 2014 evidence based guideline by the Eight Joint National Commission recommended ACE inhibitors as one of the four drugs for the treatment of high blood pressure. Cito *et al.* [40] listed such synthetic ACE inhibitor drugs used to include captopril, lisinopril and ramipril, for the treatment of cardiovascular diseases and hypertension, but their use is often associated with some side effects, such as hypotension, coughing, loss of taste, reduced renal function and angioedema [41]. Therefore, natural compounds such as ACE inhibitor peptides derived from food sources such as insects with little or no side effects may replace or support antihypertensive drugs. According to Cito *et al* [40] ACE inhibitory activity has been detected in protein hydrolysates from insect species belonging to the orders Coleoptera, Diptera, Hymenoptera, Lepidoptera and also Orthoptera. Further investigations by the team led to identification of specific ACE inhibitory peptide from silkworm *Bombyx mori* (Lepidoptera: Bombycidae), the yellow mealworm *Tenebrio molitor* (Coleoptera: Tenebrionidae), the cotton leafworm *Spodoptera littoralis* (Lepidoptera: Noctuidae) and also from the weaver ant *Oecophylla smaragdina* (Hymenoptera: Formicidae).

2.4.3 *Fibroin and sericin from silkworm and their therapeutic potentials*

Silkworm (*Bombyx mori*) larvae have two proteins necessary for cocoon formation: fibroin and sericin. Fibroin forms the fibrous weave of the cocoon and sericin a coextruded coating that acts as a matrix in the resulting non-woven composite cocoon [42]. Kunz [14] showed that the presence of hydrophobic amino acids and its antioxidant potential make it possible for sericin to be applied in the food industry and cosmetic industry. Furthermore, bioactive substances found in fibroin and sericin, exhibited a therapeutic potential for the reduction of plasma glucose level. Ryu *et al.*, [43] reported that silkworm powder has blood glucose lowering effects induced by uptake of freeze-dried 3rd day of 5th instar silkworm larval powder indicating that consumption of silk worm may assist in controlling glucose level.

Seo [44] studied the antihyperlipidemic and body fat lowering effects of silk-worm proteins with different fibroin/sericin compositions in mice fed with a high fat diet. They noted that the hypolipidemic effect was partly due to increased fecal lipid excretion, inhibition of lipogenesis and regulation of adipokine production. Their findings illustrate that silk protein particularly sericin may be beneficial in the prevention of high fat diet-induced hyperlipidemia and obesity. Seo *et al.* [44] also reported the anti-adipogenic and antiobesity effects of *T. molitor* larvae in vitro and in vivo. The results showed that the daily intake of yellow mealworm larvae powder by obese mice attenuated body weight gain by reducing lipid accumulation and triglyceride content in adipocytes, thus indicating the potential of insect bioactive compounds to induce weight loss.

Martinez-Mora *et al.* [45] stated that fibroin and sericin in silkworm *Bombyx mori* are used to stimulate wound healing, as they bring about the generation of a basal epithelium capable of replacing the epidermis of the wound. Aramwit and Sangcakul [46] stated that sericin is a wound healing agent. Ersel *et al.* [47] also reported the positive influence of sericin in the healing of incision wounds and therefore recommended sericin – based formulations in the treatment of incision wounds.

2.4.4 Antioxidants

Antioxidants also called free radicals scavengers are substances that can prevent or slow damage to cells caused by free radicals (unstable molecules that the body produces in response to environmental and other pressures) that has damaging effects on body cells. The sources of antioxidants can be natural or artificial and both are potentially beneficial in the prevention of cardiovascular and other diseases associated with free radicals in the body [48]. Felton and Summers [49] posited that insects possess a suite of antioxidant enzyme and small molecular weight antioxidants that may form a concatenated response to an onslaught of dietary and endogenously produced oxidants. The antioxidant enzymes of insects are generally composed of Catalase (CAT) and Peroxiredoxin (Prx) [50]. Antioxidant enzymes such as superoxide dismutase, catalase, glutathione transferase, and glutathione reductase have been found in insects while the roles of ascorbate, glutathione, tocopherols, and carotenoids has not being well studied in insects but may play very important antioxidant roles [49]. Roos and Van Huis [48] argued the postulations that antioxidants in food have a positive, because they opined that the activity of antioxidants is likely to change during digestive and metabolic processes. EFSA [51] stated that antioxidants in food including insects need to be tested in vivo in humans before claiming its benefits.

Antioxidants are also used as additives that preserve food from “farm to plate” and militate against oxidative deterioration of foods during processing and storage. Due to their high stability and low volatility, the antioxidants help to maintain the level of nutrients, the texture, color, taste, freshness, functionality, aroma, and appeal to consumers such as the older person, *ceteris paribus*. The possibility of extracting and using antioxidants found in insects for this purpose is yet to be reported in literature.

2.4.5 Chitin and chitosan

Chitin according to [52] is a macromolecular compound, biopolymers found in insects and crustaceans with high nutritional and health benefits. Islam *et al.* [53] described chitin as a natural mucobiopolymer, hard, white, inelastic and nitrogenous compound, composed of randomly distributed N-acetyl-D-glucosamine (N-GlcNAc) monomers. Chitin was first isolated from the cell walls of mushroom by French

chemist Henri Braconnot in 1811, and he named it “fungine” before Odier (1823) renamed it chitin. Tharsnathan and Kittur [54] noted that chitin is the second most abundant biopolymer on earth. Within annual biosynthesis of more than 100 billion tons. The exoskeleton covering the body of insects, crustaceans and some annelids contains polysaccharide chitin which accounts for 5–20% of their dry weight [55, 56]. Chitin is the second biggest available biopolymer on earth, next to cellulose and it is a primary component of the exoskeletons of arthropods [48]. Chitin serves as a raw material for making suture and wound dressing. Industrially, chitin and its products are used as a raw material for the production of hair care and skin products [57, 58]. Chitosan, though found in some types of fungi but most are obtained from chitin deacetylation. Chitosan shows more versatility than chitin due to its solubility and reactive free amino group. Chitosan is used in the food industry because they are non-toxic for warm blooded animals. It is also used as an emulsifying and gelling agent, to stabilize food. Microcrystalline chitin, addresses the problem of toxic substances consumption as it is used as flavor, colourants and dietary fibre in baked food [59].

2.4.6 Apitoxin (bee venom) and melittin

Apitoxin or honey bee venom according to [60] is a cytotoxic and hemotoxic bitter, colorless liquid containing proteins which may cause local inflammation (Table 2). Lee and Bae [4] noted that bee venom constituents include amphipathic polycationic peptides of which major ones are melittin and apamin, enzymes such as phospholipase A2, and low molecular weight compounds including active bioamines such as histamine and catecholamines, while Hoffman [61] opined that

Insect	Component	Activity
Honey bee, wasp	Melittin peptide	Kills bacteria and cancer cells, anti-inflammatory
Bumble bee	Bombolitins peptide	Antimicrobial
Honey bee, wasp	Apamin peptide	Treat muscular dystrophy and kill tumours
Honey bee, bumble bee	Mast cell degranulation peptide (MCD)	Analogues inhibit allergies
Honey bee, bumble bee, wasp	Hyaluronidase enzyme	Enhance cancer chemotherapy
Honey bee	Adolapin and other polypeptides	Analgesic and anti-inflammatory
Honey bee bumble bee, wasp	Phospholipases A1	Kills cancer cells and inhibits malaria
Wasp	Phospholipases A1	Sting diagnosis and immunotherapy
Wasp, bee	Kinins e.g. bradykinin and other neurotoxins	Pain control and neurological diseases
Beeswax, honey & royal jelly	Bio-active, oestrogenic and immunosuppressive compounds	
Bee venom	Anti-malignant, anti-inflammatory, anti-arthritic peptides, e.g. melittin	Kill cancer cells
Serrapeptase: “The miracle enzyme”		

Table 2.
Bioactive compounds in bees and wasps.

apitoxin (bee venom) is a complex mixture of several biologically active proteins and neurotransmitters such as phospholipases A2 and B, hyaluronidase, serotonin, histamine, dopamine, noradrenaline, and adrenaline, some of which can contribute to the clinical signs and symptoms of envenomation. Many authors have reported effective use of apitoxin in the treatment of a number of diseases including Oršolić [62], skin conditions [63] and even Parkinson's disease [64]. Besides, purified bee venom preparation called ApitoxR has been approved by the FDA as a subcutaneously injectable product for relieving pain and swelling associated with rheumatoid arthritis, tendinitis, bursitis, and multiple sclerosis [65].

Melittin, the major component of apitoxin about 40-50% of its total dry weight [66] is a 26 amino acid long amphipathic peptide. The 26 amino acids in melittin have an aminoterminal region that is hydrophobic, and a carboxylterminal region that is hydrophilic. This feature according to [67] enables melittin to accumulate in cell membranes, disrupting their phospholipid backbones and causing cell lysis. Melittin not only induces the lysis of a wide range of plasmatic membranes but also of intracellular. Oršolić [62] is of the view that the antibacterial effects and potential anticancer efficacy of this membrane-active peptide may be related to cytolysis following the activation of phospholipase A2, the induction of pores or perturbations in plasma and subcellular membranes, and the activation of apoptotic pathways such as those mediated by caspases and metalloproteinases membranes such as those of mitochondria.

The silkworm (*Bombyx mori*) is reported to harbor an enterobacterium of *Serratia* species which produces a substance called serrapeptase with tremendous pain relieving potential and therefore useful in reducing inflammation and pain without the usual side effect of synthetic drugs. According to [68] posited that serrapeptase also called serratiopeptidase is a proteolytic enzyme with many biological properties like anti-inflammatory, analgesic, anti-bacterial, fibrinolytic properties, thus its wide use in clinical practice for treatment of many diseases. The silkworm miracle enzyme is actually produced by a friendly bacterium found within the silkworm intestine known as *Serratia* E15. *Serratia* E15 protease proteolytic properties is responsible for dissolving the cocoon for the emergence of the moth i.e. it dissolves the casing (cocoon) which houses the pupa, for the pupa to metamorphose to adult and therefore facilitate the emergence of the adult. Proteolytic enzymes are naturally produced by the human body and other living organisms [69] and include peptidases, proteases and proteinases which are essential for many important processes in the body. They govern all of the body's metabolic functions and regulate the functioning of the body's proteins. They also play an important role in protein digestion, immune function and other vital functions.

According to the article "Silky Solution to Heart Disease" written by Wellness watchersMD, many people in recent times are deficient of proteolytic enzymes because of poor diet and unhealthy eating habits and so the body is unable to properly digest and assimilate processed foods. The result is that, as the body uses up its reserve of these enzymes, it diminishes the amount of the enzymes that are available to oversee many metabolic functions for which proteolytic enzymes are responsible; resulting in unhealthy consequences such as

- The development of chronic, low-grade inflammation, which scientists and physicians now know is one of the primary causes of all degenerative disease.
- The accumulation of waste and debris in the blood and lymphatic system.
- Diminished immune function.

- Increased risk of blood clots.
- Increased risk of infection due to bacteria, viruses, molds, and fungi.
- Increased risk of developing autoimmune diseases.

Of the above consequences, chronic inflammation is the most common problem. Chronic inflammation can cause damage to the bones, joints, cartilage and connective tissue of the body and if left unchecked can lead to gamut of conditions from allergies, arthritis, and certain respiratory conditions such as bronchitis and sinusitis, skin conditions such as eczema and psoriasis to digestive disorders such as colitis and gastritis, and even heart disease, certain types of cancer, and multiple sclerosis.

Levy [70] reported that in the 1980s and 1990s, when Japanese and European researchers compared several enzymes for potential anti-inflammatory activity, they found that serrapeptase (Serratiopeptidase) was the most effective at controlling the body's inflammatory response.

2.4.7 Cantharidin: tumour fighting substance from blister beetle (Coleopteran)

Cantharidin is a vesicant (blistering agent) produced by beetles belonging to the order of Coleoptera and the family of Meloidae [71]. It is odorless, colorless fatty acid of the terpenoid class secreted by many species of blister beetle, produced by male beetles as defense substance and given to female beetles as a copulatory gift [72, 73]. Post-copulation behavior of the female beetle involves the protection of the eggs against any potential predators by covering it with cantharidin. There are currently more than 1500 species of cantharidin-producing beetles, commonly known as *blister beetles* or *Spanish fly*, variable in color, measure up to 2.5 cm in length and neither bite or sting [74].

Cantharidin has been available synthetically since the 1950s, topical applications of cantharidin have been used predominantly as a treatment for cutaneous warts [72, 73]. In 1962 however, marketers of cantharidin failed to produce sufficient efficacy data, resulting in the FDA revision of approval of cantharidin. In 2004, FDA accepted cantharidin, the blister-causing oil found in several families of beetles as a treatment for warts and other skin problems. Moed [74] stated despite FDA directive for the removal of cantharidin from market. Some dermatologists continue to use either proprietary or non-proprietary formulations. Recent studies in cell culture and animal models have demonstrated powerful tumor-fighting properties of cantharidin. Wang [75] cited in [74] noted that cantharidin was used historically for furuncles, piles, ulcers, venomous worms and tuberculosis scrofulderma, so [74] stated that it was used orally for abdominal cases, rabies, abortifacient and anticancer agent.

Further studies showed that cantharidin contains something known as a protein blocker. Protein blockers are used to fight infections, and appeared to attack only the infected cells. Then scientists discovered it also attacked viral cells. Now studies show that the blister beetle secretions attack hostile cells – including cancer. There are studies that indicate blister beetles might be used to “battle tumors and in chemotherapy treatments. Studies from many researchers including [76–79] suggest that the tumor growth inhibitory properties of cantharidins could be attributed, at least in part, to anti-angiogenic activity. Cantharidin and some of its derivatives inhibited the proliferation, migration, and invasion of, as well as capillary-like structure formation by cultured endothelial cells.

2.4.8 *Solenopsis* (Formicidae: Hymenopterans)

The word *Solenopsis* refers to the venom of stinging ants precisely fire ants belonging to the genus *Solenopsis*. The venom is water-insoluble and non proteinaceous and contains hemolytic factors that cause the release of histamine and other vasoactive amines. The genus has over 200 species, in the order Hymenoptera, family Formicidae and subfamily Myrmicinae, but Fitzgerald [80] stated that two are of major medical importance: *Solenopsis richteri* (black imported ant) and *Solenopsis invicta* (red imported ant). *Solenopsis richteri* originated from eastern Argentina and Uruguay [80] while *Solenopsis invicta* is a native of the Mato Grosso region of Brazil. The venom from these fire ants is Solenopsin A (trans-2-methyl-6-n-undecylpiperidine) a piperidine alkaloid with cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, antifungal, anti-HIV, cardiodepressant and neurologic actions [81]. Arbiser [82] showed that solenopsin A potently inhibited the growth of SVR cells (a transformed murine endothelial cell line) by inhibiting endothelial-specific signaling. This suggested that it has anti-angiogenic activity, owing to its selective inhibition of a series of kinases involved in angiogenesis, most notably phosphatidylinositol-3-kinase (PI3K) and its downstream effector Akt (Protein kinase B (PKB)), a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration).

Studies from Emory and Case Western published in Scientific Reports showed elements in the fire ant venom capable of reducing skin thickening and inflammation and thus a useful treatment for psoriasis condition (a chronic immune system –based disease that manifests in abnormal patches on the skin). The toxic component of *Solenopsis* venom is a lipid-like molecule called ceramides. Mencarelli [83] stated that ceramides are fatty acid amides of sphingosine, which play a crucial role in homeostasis of the skin and other organs. So under certain conditions they are converted to Sphingosine-1-phosphate (S1P) which causes inflammation that is usually associated with the sting. Thus scientists have created a version of fire ant venom's solenopsin (via genetic engineering) that cannot be converted to S1P and is currently used as anti-inflammatory product.

2.4.9 Extract from Chinese black ant (*Polyrhachis vicina* Roger)

The Chinese black ant (*Polyrhachis vicina* Roger) according to [84] belongs to the Formicidae, Hymenoptera, Insecta in zootaxy and is widely distributed in subtropical, southeast China, India, Malaysia, Sri Lanka and Bangladesh [84]. The Chinese traditional healers were the first to use extract of black mountain ants in preparation of medicine which they call “King of herbs” even though it is an extract from black Chinese mountain ants. The ants live up high in mountains and are often found among ginseng roots. Chinese men use the tonic from the black mountain ant for treatment of impotence and fatigue. Today, modern science has proven that the extract is a rich source of energy, vitamins and minerals especially those necessary for overall sexual health. *Polyrhachis* is a highly concentrated source of protein (42 - 67% by mass), zinc (highest amount of zinc in all known living organisms), vitamins B-12, B-1, B-2, D, and E [85]. All of these substances are vital for health and sexual performance. The rich content of zinc is one of *Polyrhachis* exceptional qualities because zinc is a powerful natural antibiotic which kills many pathogens including bacteria and viruses and at the same time strengthens the immune system. Tang and Dai [84] stated that *P. vicina* had the potency to potentiate immune response in animals. Besides, the anti-inflammatory, hepatoprotective, immunoregulatory and analgesic activities displayed by the Chinese black ant is documented by [86].

Polyrhachis vicina Roger has long been found to be very rich in ecdysterone, the growth hormone of insects, which has a strong protein anabolic effect, and so contribute to the growth promoting effect of *Polyrhachis vicina* [87]. Ecdysterone is structurally similar to androgens (male hormones such as testosterone), and many suggest its use as a safer alternative to anabolic steroids.

Black ant is also reported to contain superoxide dismutase (SOD) [85, 88]. Superoxide dismutase is a powerful antioxidant made in the liver to support oxidation for energy production. It also contains substantial amounts of the mineral selenium, used by the liver to make SOD, further increasing stress-tolerance and stamina. In addition high amounts of vitamin E in black ant increase the stress – resistance benefits.

FDA laboratory analysis showed that the black ant contains sildenafil, the active ingredient in the FDA approved prescription drug viagra, used to treat erectile dysfunction (ED). Viagra works by increasing blood flow into erectile tissue by prompting blood vessel dilation. In addition to improving blood circulation to the extremities, black mountain ants increase androgen levels (a sexual hormone) responsible for regulating sexual desire in the blood. In addition to being a potential alternative to Viagra, these ants are also being studied for their usefulness in combating cancer. The need for enhancement of sexual performance stems down from the fact that sexual performance is based on the overall health of the body. Thus sexual performance of men is weakened and fatigued by nutrient deficiencies especially a lack of protein. Such men will be too tired and quite possibly be suffering from a lack of testosterone due to nutritional deficiencies affecting the hormone levels. Natural supplements such as *Polyrhachis* ant (Black ant) extract has proven to be a real solution because they are not drugs and so can improve sexual performance naturally and do not present worrisome side effects unlike synthetic drugs like Viagra associated with many side effects.

2.4.10 *Polybia* MP1 from Brazilian social wasp (*Polybia paulista*): a killer of cancer cells

Michelle Roberts Health editor of online BBC news of September 1, 2015 reported on the toxin in the sting (i.e. venom of the wasp) of Brazilian social wasp (*Polybia paulista*) that kills cancer cells without harming normal cells. The cancer-targeting toxin in the wasp called MP1 (*Polybia*-MP1) [89]. According to a new Brazilian research published in the Biophysical Journal, a molecule called MP1 kills the cancer cells by “creating holes on their lipid membrane.” These holes make molecules that cancer thrives on, to leak out. Cancer cells cannot survive without these molecules and so they die within seconds. Meanwhile, the normal cells are perfectly safe as MP1 is very selective and does not harm them.

Wang *et al.* [90] stated that *Polybia* MP1 is a short cationic alpha helical amphiphilic peptide that has selective toxicity toward cancer cells but no haemolytic activity. Its target selectivity according to [90] is based on the binding preference to membranes containing anionic phospholipids by electrostatic driving. These promising findings led to anti-cancer therapies involving MP1 being currently studied. According to [91, 92] cancer cell membranes are now known to lose the asymmetric transmembrane distribution of phospholipids that is observed in healthy cells. In healthy mammalian cells, the anionic aminophospholipid PS (phosphatidylserine) is predominant in the inner membrane leaflet and zwitterionic phospholipids are predominant in outer membrane leaflet. In such cells, the phospholipid asymmetry is maintained by a family of aminophospholipid translocases that catalyze the transport of PS from the outer to the inner membrane leaflets [93]. However, in

apoptotic and cancer cells, PS is found to also be located in the outer monolayer of the plasma membrane in significant proportions [91, 92].

Zhao *et al* [94] demonstrated that Polybia-MPI displays potent antibacterial activity against both gram-positive and gram-negative bacteria. Wang *et al.* [95, 96] further stated that polybia-MPI has potent antifungal and antitumor activity and low toxicity to human red blood cells and normal fibroblasts.

2.4.11 Natural antibiotic from cockroach brain

The ability of bugs and other flies to survive unscathed in dirty environments with a heavy load of pathogenic microbes has attracted the interest of microbiologists and other researchers [97]. Fazackarley [98] reported the findings of Simon Lee and Naveed Khan, an Associate Professor of Molecular Microbiology presented to Society for General Microbiology's autumn meeting in Nottingham and published on the University of Nottingham website, in which the researchers described how his group identified nine different molecules in the brain tissues of the cockroach (*Periplaneta americana* (Blattidae) and desert locust (*Schistocerca gregaria*) that were toxic to bacteria. The group found that the tissues of the brain and nervous system of the insects were able to kill more than 90% of Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*, without harming human cells. Simon Lee stated that these molecules could eventually be developed into curative applications for the treatment of E. coli and MRSA infections that are increasingly resistant to current drugs. These new antibiotics could potentially provide alternatives to currently available drugs that may be effective but have serious and unwanted side effects. Yu *et al.* [99] and He [100] reported that pharmacological research has revealed that *P. americana* has anti-tumor effects and is able to enhance immunity, promote tissue repair, stabilize blood pressure, improve microcirculation, protect the liver, and act as an anti-inflammatory, anti-bacterial, and anti-viral agent as well as an analgesic and anti-oxidant. Dai *et al.* [101] on the other hand noted that the active ingredients isolated from *P. americana* have been developed into clinical drugs in China namely "Xiaozheng Yigan tablet", "Kangfuxin liquid", "Ganlong capsule" and "Xinmailong injection". Xiaozheng Yigan tablet is an oral tablet with potent anti-tumour effects and anti-bacterial activity [102]. Ou *et al.* [103] cited in [102] noted that the drug reduces liver inflammation, promotes the recovery of liver function, and reduces liver fibrosis in patients with hepatitis-B virus. *Periplaneta americana* (Blattidae), is also used for a variety of other conditions including: heartburn, asthma, stomach ache, intestinal colic, earache, alcoholism, epilepsy, vomit, boil, hemorrhage, bronchitis, diarrhea, gonorrhea, panaris, cancer, stroke, burns and menstrual cramps.

2.4.12 Other bioactive substances found in insects

Many other bioactive substances found in insects are listed in the **Table 3**.

2.5 Arthropods in Orthodox medicine

Blood-Feeding Insects and Prevention of clot formation

For long blood sucking insects have always been associated with diseases they transmit: Mosquitoes- malaria, Tse tse fly- trypanosomiasis, tick – East coast fever. The use of insect in traditional healing by practitioners of Eastern medicine in prevention of blood clot formation or thrombosis was not given much consideration. However, in recent times, some proteins in the saliva of blood sucking insects are found to possess anti-coagulation properties and these are

Bioactive substance	Insect	Properties	Author
Eumentin	Eumenine wasp (<i>Eumenes rubronotatus</i>)	Antimicrobial	[104]
Mastoparans	Vespid wasps	Antibacterial, antiviral, Antitumor,	[105–107]
Termicin and spinigerin	Termitidae <i>Pseudocanthotermes spiniger</i> Sjostedt, <i>Nasutitermis corniger</i> Motschulsky,	Antimicrobial peptides	[108]
Anticoagulants in the saliva of blood sucking insects a. Simukunin and analogues b. Tablysin-15, c. Anophelin, d. Nitrophorin-2 (or prolixin S) is a 20-kDa lipocalin	Many blood sucking insects Tablysin-15 is produced by the horsefly <i>Tabanus yao</i> Macquart, 1855 <i>Anopheles albimanus</i> C.R.G. Wiedemann, (Culicidae Kissing bug <i>Rhodnius prolixus</i> Stal, 1859	Prevent formation of blood clot	[109–111]
Termicin and spinigerin	<i>Pseudocanthotermes spiniger</i> Sjostedt, and <i>Nasutitermis corniger</i> Motschulsky,	Antimicrobial and Anti-parasites	[108]
Pierisins 1a, 1b, 2-5	<i>Pieris</i> (Pieridea) including the cabbage butterfly <i>P. rapae</i> Linnaeus	Antimicrobial and Anti-parasites	[112]
Myrmexins	<i>Devil tree ant</i> (<i>Pseudomyrmex triplarinus</i> Weddell) In Nigeria it is found on two main trees : Local pear (<i>Dacryodes edulis</i>) and African star apple (<i>Gambeya albidium</i>)	Extract of the venom from <i>Pseudomyrmex</i> spp. decreases pain and inflammation in patients with rheumatoid arthritis and reduces swelling	[113]
Isocarbostyryl alkaloids	Texas grasshopper <i>Brachystola magna</i> Girard	Antitumor	[114]

Table 3.
Other bioactive substances found in insects.

found useful in modern or orthodox medicine. According to [115] arthropods in at least 23 different families or orders distributed between insect and arachnida feed on vertebrate blood and they are able to do this despite constraints imposed by a sophisticated array of hemostatic defenses. Their ability to do this is based on the presence of a wide range of antihemostatic molecules in their saliva including vasodilators, antiplatelet factors and anticoagulants. Leitch [116] reported that the molecule in the mosquito spit can thin blood clots. According to him, scientists are learning how to exploit the anti-clotting abilities of molecules in mosquito saliva and use them to create treatments for disorders like stroke or deep vein thrombosis. Professor Richard Payne an ARC Future Fellow in the Faculty of Science noted that this protein secreted in the saliva of mosquito precisely anopheles mosquito is called anophelin and is designed to prevent the host organism's blood from clotting, so the mosquito can access the host's blood for meal. He posited that anophelin targets and binds the central host blood coagulation enzyme thrombin and therefore prevents clotting. Further studies by scientists have shown that sulfate modification of the protein significantly improved its anticoagulant activity.

Today, the anti-coagulant activity of many more arthropods have been reported in literature [117]. Perez de Leon *et al.* [118] reported on the anticoagulant activity in the salivary glands of the insect vector *Culicoides variipennis sonorensis*. Research fellows at University of Sydney opined that by mimicking the anticlotting properties of the proteins in a mosquito's saliva, scientists can develop new drugs to treat conditions such as deep vein thrombosis or stroke.

These compounds in the saliva of blood feeding insects are capable of increasing the ease of blood feeding by preventing coagulation of platelets around the wound and provide protection against the host's immune response. Most of all, over 1280 different protein families have been associated with the saliva of blood-feeding organisms [119]. Ratcliffe *et al.* [120, 121] showed that most of them are pharmaceutical compounds including: inhibitors of platelet aggregation, ADP, arachidonic acid, thrombin, and PAF, anticoagulants, vasodilators, vasoconstrictors, antihistamines, sodium channel blockers, complement inhibitors, spore formers, inhibitors of angiogenesis, anesthetics, AMPs and microbial pattern recognition molecules. Champagne [115] stated that the vasodilators include amines, prostaglandins, peptides and proteins, platelet aggregation inhibitors include nitric oxide, prostaglandins, apyrase molecules that sequester ADP and a range of peptides and proteins, while the anticoagulants include a wide range of inhibitors that target thrombin and factor Xa, as well as proteins that disrupt the "tenase" prothrombinase and tissue factor/FIIa complexes.

2.5.1 Maggot therapy in wound treatment

Maggot therapy according to [122] is the application of live fly larvae to wounds in order to aid in wound debridement (cleaning), disinfection and/or healing. Maggot infestation of the wound of a living vertebrate host is called myiasis. Sun [123] defined maggot therapy as a type of biotherapy involving the introduction of live, disinfected maggots into the non-healing skin and soft tissue wound (s) of a human or animal for the purpose of cleaning out the necrotic (dead) tissues within a wound (debridement) and disinfection.

The effectiveness of maggot therapy is based on the proper control of the system. Such proper control of the system involves selecting the appropriate species and strain of fly (the species most commonly used is *Lucilia (Phaenicia) sericata*), disinfecting the larvae, using special dressings to maintain the larvae on the wound, and integrating quality control measures throughout the process. There are also conditions expected in the wound for the maggot to thrive: the wound must be moist, exuding with a good flow of oxygen, thus not all wound types are suitable for maggot therapy. This means that dry, open wounds of body cavities do not provide a good environment for maggots to feed. Dry wounds however can be made suitable for maggot therapy by moistening it with saline soaks, for at least 48 hours. Tian *et al* [124] reported that maggot therapy improves healing in chronic ulcers, diabetic foot ulcers, and venous leg ulcers. FDA in 2004 cleared maggots from common green bottle for use as a medical device in the US protocol for the treatment of non-healing necrotic skin and tissue wounds, pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic or post-surgical wounds.

Even though reports of the usefulness of maggot therapy in wound healing is common in literature, patients and doctors still find maggot therapy very absurd. Sherman [122] reported that clinicians are often more disgusted with maggot dressings than are patients. Petherick *et al.* [125] study in this regard showed that approximately 25% of patients offered larval therapy for treatment of chronic leg ulcers preferred alternative treatments rather than maggot. Similarly, [28] found only 77% agreeing to leg ulcer treatment with maggots [126]. Health professionals

are also skeptical about prescription of maggot therapy, but [127] is of the view the negativity is often replaced by acceptance as of the results delivered.

2.5.2 Apitherapy

Apitherapy according to [128] is the practice of using bee products such as honey, pollen, propolis, royal jelly and bee venom for disease prevention and treatment purposes. Cherbuliez [129] described it as the science and art of using honeybee products to maintain health and assist the individual in regaining health when sickness or accident interferes. The Apimondia Standing Commission for Apitherapy that works for the promotion of the use of bee products for apitherapy defined apitherapy as a medical concept, based on scientific foundations corroborating traditional knowledge, including: bee production procedures aimed at medical development. According to the archeologist Giorgog Marovfrydis, who was also a beekeeper, the first known testimonial on the use of bee products for therapeutics dates back to 2100BC which refers to a recipe written in cuneiform script on Sumerian clay plate found in Euphrates valley.

There is also biblical and Quranic evidence of God's directive on the use of honey. Exodus 3: 8, Exodus 33:3 Exodus 13:5, Leviticus 20:24, Numbers 13:27, Numbers 16:14, Deuteronomy 6:3, Deuteronomy 31:20, Joshua 5:6 all showed the description of the Promised Land as a land flowing with milk and honey. Deuteronomy 8:8 described it as a land which abounds in olive oil and in honey. Besides, the Bible has many other references on the divine directive for mankind to eat honey.

Prov. 24:13 "My son, eat thou honey, because it is good and honeycomb which is sweet to thy taste" (KJV)

Prov. 25: 27 "It is not good to eat much honey, so for men to seek glory, their own glory, causes suffering and is not glory"

Matt 3:4 and Mark 1:6 talked of John the Baptist eating locust and wild honey.

Koran Sura 16 stated that honey the origin and therapeutics properties of honey: "It comes from their bellies, a liquid of various colours with healing for mankind". Apart from the medicinal properties of honey, many other products are mentioned in literature: pollen, propolis, wax, royal jelly and venom.

2.5.3 Honey

Manisha deb Mandal and Shyamapada [130] reported on the antimicrobial properties of honey. The antimicrobial property is due to its enzymatic production of hydrogen peroxide, low pH, and high content of sugar (high osmolarity). According to [131] the most common bacterium known to be inhibited by honey is *Streptococcus pyogenes*; another bacterium that is reported to be inhibited by honey is *Helicobacter pylorum* (a causative factor in ulcers). Abd-ElAal et al., [132] showed that honey has a more pronounced inhibitory effect (85.7%) on gram-negative bacteria (*Pseudomonas aeruginosa*, *Enterobacter spp*, *Klebsiella spp*). They also reported a 100% inhibition was observed in the case of gram positive methicillin-resistant *Staphylococcus aureus*.

As stated above three factors are responsible for the antimicrobial properties of honey: enzymatic activities, low pH and high content of sugar. One of the enzymes present in honey is glucose oxidase, produced by the bees' hypopharyngeal (head) glands. Upon dilution, the enzyme is activated and generates gluconic acid and hydrogen peroxide. Secondly, the high osmotic potential of honey is due to its high sugar concentration: that is osmotic effect, which can lead to the breakdown of bacterial membranes, thus inhibiting microbial growth. Honey's low pH also makes it difficult for bacteria to thrive in the medium.

Medical values of honey include its wound healing capability, oral health, treatment of pharyngitis, cough and gastrointestinal disorder, peptic ulcer, gastroesophageal reflux disease, gastroenteritis, constipation and diarrhea, liver and pancreatic diseases etc.

2.5.4 Bee pollen

Pollen, the male gametophyte of flowering plants is high energy material which is collected by insects and stored as food [133]. Bee pollen refers to the flower pollen that collects on the legs and bodies of worker bees as they collect pollen for the colony. It is rich in sugars, proteins, minerals, vitamins and fatty acids. It also includes nectar and bee saliva. The chemical composition of pollen varies depending on the flowers from which the pollen was collected. Kielislszek [134] noted that bee pollen recently gained traction in the health community because it is loaded with nutrients, amino acids, vitamins and other 250 active substances. According to [133]), pollen has been used medically in the treatment of prostatitis, bleeding, stomach ulcers and some infectious diseases, although medical practitioners are yet to reach a compromise regarding these claims. Salles *et al* [135] stated that the Federal Ministry of Health in Germany recognizes bee pollen as medicine. Denisow *et al* [136] also stated that bee pollen is loaded with a wide variety of antioxidants including flavonoids, carotenoids, quercetin, kaempferol and glutathione.

2.5.5 Propolis

Propolis also called bee glue is a sticky substance used by worker bees to cement cracks in the hive. Almeida and Menezes [137] noted that the word propolis came from two Greek words: Pro (meaning “in defense of”) and Polis (meaning “city”). Propolis are resinous substances, gummy in nature, collected from plants by the bees and used as cement to seal cracks or open spaces in the hive, sterilize the queen bee posture site, and to mummify insect invaders [137]. Ramos and Miranda [138] also described propolis as a honeybee product with a very complex chemical composition, made by gummy and balsamic material collected by bees from sprouts, flower-buds, trees and other vegetal-tissue resinous exudates. Although the chemical composition of propolis has been known for long. Ramos and Miranda [138] opined that correlation of propolis chemical composition with its pharmacological activities started forty years ago. Volpi [139] reported that twelve different flavonoids found in propolis namely pinocembrin (antifungal factor), acacetin, chrysin, rutin, luteolin, kaempferol, apigenin, myricetin, catechin, naringenin, galangin and quercetin, two phenolic acids (caffeic and cinnamic acid) and a stilbene derivative called resveratrol. Besides, propolis also contain important vitamins: vitamin B1, B2, B6, C and E, as well as useful minerals Magnesium, Calcium, Potassium, Sodium, Copper, Zinc, Manganese, Iron and a few enzymes such as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase and acid phosphatase [140].

Health benefits of propolis have been reported by many authors including oral health, gynecological care, oncological treatment, dermatological care and treatment for gastrointestinal disorder. Wieckiewicz and Miernik [141] described the possible uses of propolis in treatment of various diseases of the oral cavity. Sneviranne *et al* [142] stated that the mouth environment is rich in bacterial flora, thus inhibition of microorganisms in the oral cavity could be its mode of action. However, other researchers reported that it works by inhibiting the enzyme glucosyl transferase of the bacterium *Streptococcus mutans*; a bacterium that produces lactic acid in the mouth that decays tooth enamel. Pereira [143] also showed that propolis

restricts bacterial plaque development and periodontitis-causing pathogens because of its antibacterial properties. Today some companies include propolis in mouth-wash, toothpaste and chewing gums as a remedy to toothache [144].

Again, owing to the fact that bacteria proliferation in the vagina, overgrowth of vaginal pathogens such as yeast like fungi, depletion of *Lactobacillus* spp., and elevated vaginal pH are the main causes of vaginal diseases. A study conducted by [145] on the application of 5% aqueous propolis solution resulted in an improvement in vaginal well-being. Pasupuleti [146] stated that in addition to providing antibiotic and antimycotic actions, propolis provides early symptomatic relief due to its anaesthetic properties.

On the issue of oncological treatment, Pasupuleti [147] reported that propolis has potential towards human breast cancer treatment due to its antitumor activity by inducing apoptosis on human breast cancer cells. Benguedouar et al [146] stated that galangin, a common flavonoid found in Algerian propolis, induced apoptosis and inhibited melanoma cells in vitro.

Pasupuleti [147] reported the use of propolis in dermatological products. According to them, its use in skin care products is based on its anti-allergy, anti-inflammation, anti-microbial properties and promotive action on collagen synthesis. Amad Oryan *et al* [148] showed that an important factor in impaired wound healing is biofilm formation and that propolis antimicrobial agents can reduce biofilm generation, thereby resulting in accelerated healing process. Propolis is also reported to reduce activity of free radicals (ROS) in the wound bed favoring the repair process. Pasupuleti [147] also reported that its effect on collagen metabolism by increasing both type I and type III collagens in tissues.

2.5.6 Royal jelly

Viuda-Martos et al [149] defined royal jelly as a thick and milky secretion produced by the hypopharyngeal and mandibular glands of young worker bees (*Apis mellifera*) used to feed the larvae. Literature reports showed that worker bees and queen bees start life as identical eggs laid by the parent queen, but whether the egg develops into a worker bee or a queen bee depends on the way each of them is fed. Queen bee larvae are fed with copious amounts of royal jelly and so differ in many respects from adult worker bees. This development has aroused the interest of researchers on the composition of royal jelly that has made it capable of determining the nature of a bee. Viuda-Martos *et al.* [149] also noted that royal jelly has a high content of bioactive compounds consisting of peptides such as royalisin, jelleines, aspimin and royalactina; polyphenols, principally phenolic acids, flavonoids and lipids such as 10-Hydroxy-2-Decenoic acid. Ramadan and Al-Ghamdi [150] listed other bioactive compounds in royal jelly to include fatty acids, proteins, adenosine monophosphate (AMP) N1 oxide. Royalactin is the main compound in royal jelly that allows the morphological change of a larva into the queen bee [151]. It is therefore called a superfood and is the main reason for the longevity of the queen bee compared to the other bees. Strant [152] stated that royal jelly being a secretion of worker bees is of a more constant composition compared to other honey bee products. In her report, she also stated that the most interesting property of royal jelly is 10-hydroxy-2-decenoic acid and vitamins in the B complex which include thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, biotin and folic acid, but little vitamin C, while vitamin A and E are absent or nearly so, vitamin D and K are probably also absent. Royal jelly was also reported to possess health promoting properties including antioxidants, anti-inflammatory, antibacterial, anti-tumour, hypocholesterlemiant, hepatoprotective, vasodilative and hypotensive [149].

The usefulness of royal jelly in wound healing has been reported by many authors. A study by researchers at Ain Shams University, Cairo in 2016 attributed the wound healing potentials of royal jelly to its ability to eradicate Methicillin Resistant *Staphylococcus aureus* infection [153] but the study did not mention involvement of any peptide. However recent research by Slovak Academy of Science found the peptide defensin-1-peptide as the factor responsible for wound healing ability of royal jelly. Defensin-1-peptide heals wounds by increasing keratinocyte migration and keratinocyte is largely responsible for epithelialization of the skin after injury [154].

Hethir Rodriguez an herbalist and a nutritionist, the Founder and President of Natural Fertility Info.com. reported on three studies to buttress the effect of royal jelly in reproductive health. First a study done in Japan and published in 2007 in the journal *Evid Based Complement Alternat Med.* which showed that Royal Jelly has the propensity to mimic human estrogen, similar to that of plant phytoestrogens. Estrogen is essential for healthy bone formation and gene expression, and is vital for a healthy menstrual cycle. The study also showed a potential for increased size of uterine cells in the rats studied.

Another study out of Kuyushu University in Japan, aimed to see if Royal Jelly could combat BPA growth-promoting effects on human breast cancer MCF-7 cells. BPA (bisphenol A) is a harmful chemical used in plastics that is a known xenoestrogen. The results of the study showed that Royal Jelly inhibits the stimulated growth of BPA on MCF-7 cells. Not only has BPA been linked to breast cancer, it has also been linked to poor egg health.

The third study reported is that of additional promising rat study of Iran, published in the *International Journal of Fertility and Sterility* which found that Royal Jelly “promotes folliculogenesis [the maturing of follicles in an ovary] and increases ovarian hormones...” Thirty two female rats were divided into four groups, three control groups receiving either 100, 200 or 400 mg/ kg of body weight daily for 14 days. Rats in the Royal Jelly consuming control groups had increased levels of estradiol and progesterone, increased uterine and ovarian weights, as well as a significant increase in mature follicles and corpora lutea (more than one corpus luteum). Serum antioxidant levels were increased and nitric oxide levels decreased.

2.5.7 Bee venom

Bee venom is the poison in the bee sting that makes it very painful. It is a colourless, acidic liquid which the bees excrete through its stinger into the body of any intruder assumed to threaten its life. Barish [155] reported that an average adult can withstand 1000 sting whereas 500 stings could kill a child, but for an allergic person, one sting can cause death due to anaphylactic reaction (a life threatening allergic reaction in which blood pressure falls and airways closes). Africanized honey bees, also called killer bees, kill their victim in swarms. Research into the chemical composition of bee venom showed that it contains a complex mixture of proteins and amino acids, enzymes, sugars and lipids, polypeptides [156]. Melittin, a polypeptide compound, made up of 26 amino acids, comprising 50% of the dry weight of bee venom, has been shown to be antiviral, antibacterial and anticancer [156, 157]. Bee venom also contains the peptides: apamin and adolapin which possess anti-inflammatory and pain relieving properties.

2.5.8 Medicinal properties of termite

Medicinal properties of termite has been investigated by a number of researchers, [158] investigated the antibacterial ability of the termites mostly used by South

Indians for treating diseases associated with microorganism and found that 90% of alcohol extracts of three species of subterranean termites, namely; *Odontotermes formosanus* Shiraki, *Microtermes obes* Holmgren and *Macrotermes estherae* (Desneux) were effective against bacterial diseases. Nine termite species were recorded to be used for therapeutic purposes. Africa is the continent with the highest number of usage, followed by America and Asia respectively. The results showed that termites are useful for medicinal and food purposes to humanity. Alves and Alves [159] also reported that *Microcerotermes exiguus* contains antiviral properties and as such effective for treating cold, cough, hoarseness, asthma, catarrh, bronchitis, influenza, flu, whooping cough, sore throat, sinusitis and tonsillitis.

3. Conclusion

From the foregoing, the bioactive substances from arthropods are so enormous that it can no longer be overlooked or relegated to the background. Arthropods now hold the future of orthodox and traditional medicine. To me the discoveries on the medicinal, pharmaceutical and nutraceutical values of arthropods are quite indisputable, so the next line of action will be the utilization of the named arthropods in the production of drugs and other pharmaceutical as well as cosmetic products. I therefore recommend that research torchlight will be on large scale production of these insects, extraction of the bioactive ingredient and incorporation/ utilization in production of drugs especially for challenging diseases like cancer.

Conflict of interest

None.

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